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博士学位论文

Smurf1介导的RhoB泛素化降解在DNA损伤引起的细胞凋亡过程中的作用

Role of Smurf1-mediated RhoB degradation in DNA damage-induced apoptosis

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摘 要

Rho家族小分子GTP酶做为细胞内许多信号转导通路中重要的分子开关，在调节细胞骨架、细胞极性、细胞运动、基因表达、细胞生长分化、膜泡运输、以及细胞周期等细胞生物学过程中发挥着重要作用。RhoA、RhoB和RhoC是Rho家族中的一个重要的亚家族，它们在氨基酸序列上具有很高的同源性并且都参与细胞骨架的重塑过程。然而，和RhoA、RhoC不同的是，RhoB可以做为抑癌基因参与应答由DNA损伤引起的细胞凋亡过程。在紫外线照射或抗癌药物等引起的DNA损伤的情况下，RhoB做为早期应答基因能够迅速表达并介导凋亡过程的发生。RhoB基因缺失小鼠的胚胎成纤维细胞（MEF）经放射线照射或抗癌药物阿霉素处理后，其细胞凋亡的比率明显低于野生型对照组。过表达RhoB的细胞具有生长缓慢的特性并更易于发生细胞凋亡。临床样本也显示随着肿瘤恶性程度的增加，RhoB蛋白的表达水平随之下降，提示RhoB介导的凋亡过程在癌症发生中可能发挥总要作用。然而，RhoB介导细胞凋亡的分子机理以及RhoB本身水平的调控的分子机制还很不清楚。

经典的Rho蛋白活性的调节方式是通过与GTP或GDP两种不同形式的鸟嘌呤核苷酸来调控的。然而，最近的研究结果表明一些Rho家族的成员也可以通过泛素化修饰来影响其蛋白水平与生物学活性。在本文的研究中，我们发现，与泛素化调节RhoA相似，C2-WW-HECT家族E3泛素连接酶中的Smurf1也可通过泛素化修饰来调控RhoB的蛋白水平，然而却对RhoC没有影响。有趣的是，与泛素化降解RhoA不同，Smurf1泛素化降解RhoB对细胞骨架的重塑过程没有明显的作用，却对细胞应答紫外线照射和化学试剂诱导的DNA损伤所引起细胞凋亡起着至关重要的作用。在DNA损伤的情况下，Smurf1通过增强自身的降解，使得RhoB的蛋白水平显著增加，进而引起细胞凋亡。Smurf1介导的RhoB泛素化降解对于细胞应答DNA损伤具有重要作用：在敲低内源Smurf1的情况下，细胞对于DNA损伤的敏感性大大增加，而在过量表达Smurf1的情况下，细胞对于DNA损伤的耐受程度明显增加，显著地抑制了DNA损伤所诱导的细胞凋亡。因此，本文发现了一个通过E3泛素连接酶Smurf1调控RhoB蛋白稳定性从而调节细胞应答DNA损伤所引起的凋亡的分子机制，为进一步深入了解与RhoB相关的肿瘤发生的分子机理提供了新的思路，并为以RhoB为分子靶点的可能的肿瘤治疗提供

了理论基础和实验依据

关键词：E3泛素连接酶；Smurf1；RhoB；DNA损伤；凋亡

Abstract

As molecular switches, Rhofamily small GTPasesplay key roles in many signal transduction pathways that regulate cytoskeleton, cell polarity, cell migration, gene expression,cell growth and differentiation, vesicular transport, and cell cycle. RhoA, RhoB and RhoC,are three close family members that belonge to the Rho family and participate in cytoskeleton remodeling. Although they share high homology in amino acid sequence, RhoB has different function from RhoA and RhoC. It has been reported that RhoB may take part in DNAdamage-induced apoptosis as a tumor suppressor gene. In the event of DNA damage caused by UV or anti-cancer drugs, RhoB expression is quickly up-regulated, which is important for apoptosis process. Mouse Embryonic Fibroblast cell (MEF) isolated from RhoB-null mouse had lower apoptotic rate than control groups after UV irradiationor doxorubicintreatment. Cells ectopically expressing RhoB exhibit growth retard and are apt to apoptosis. Clinical samples also demonstratedthat correlated with the malignancy of tumors, RhoBprotein levels were significantly down-regulated, indicating that RhoB-mediated apoptosis may play important roles in cancer development. However, the molecular mechanism underlying is still obscure.

Classical regulation of Rho proteins is dependent on their binding status with GDP or GTP. Recent reports demonstrated that ubiquitin modification could also affect protein levels of Rho GTPase and their biological functions. In our research, we found that, similar with RhoA, RhoB but not RhoC could also be ubiquitinated by Smurf1, a member of C2-WW-HECT E3 family ubiqutin ligase.In contrast to Smurf1-mediated degradation of RhoA, degradation of RhoB by Smurf1 have no apparent effect on the remodeling of cytoskeleton. Interestingly, Smurf1-dependent degradation of RhoB is essential for DNA damage-induced apoptosis. During treatment of UV or chemical reagents, Smurf1 is down-regulated, which

subsequently up-regulated protein levels of RhoB that is important for cell apoptosis. Cells were much more susceptible to DNA damage when endogenous Smurf1was knocked-down.When Smurf1 was overexpressed, cells were substantially more resistant to DNA damage. Thus, we identified a novel mechanism that RhoB degradation by Smurf1 determines the susceptibility of cells to DNA damage: In addition, our discovery pointed a road for further research on the molecular mechanism of RhoB-involved cancer development and potential cancer therapy way using RhoB as a target.

Keywords: E3 ubiquitin ligaseSmurf1RhoBDNA damageapoptosis

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